

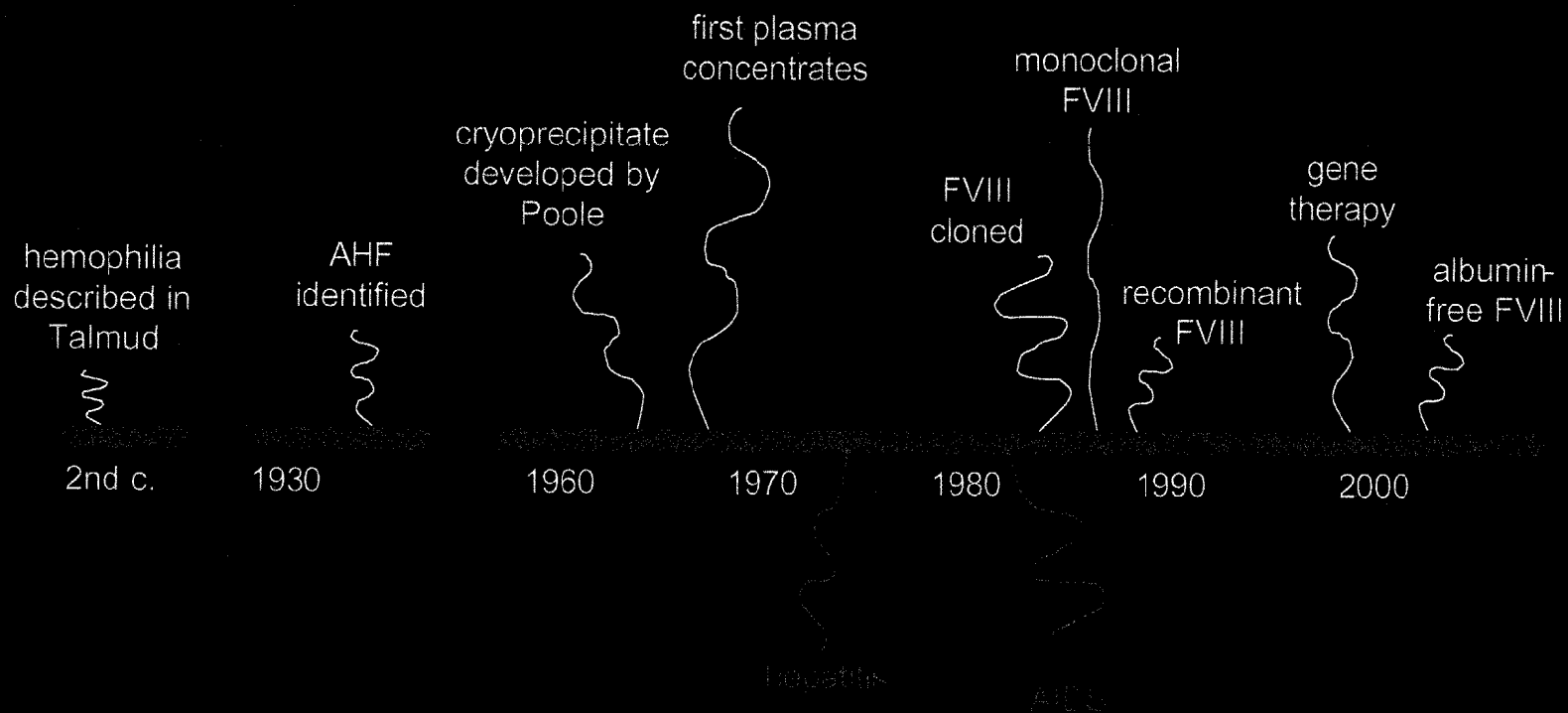
ISTH Rationale of Recommendations for Use of Previously Treated Patients in Clinical Trials

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Advances in Hemophilia



Initial Trials of Ultrapure Concentrates

It was hoped/expected that monoclonal antibody purified plasma and recombinant concentrates of FVIII and FIX would be free of blood borne infectious agents ...

... the clinical evaluation of the new concentrates was carried out in two phases: first in previously treated patients to test efficacy and second in patients who were uninfected to test for viral safety.

Prevalence of Inhibitors in Recombinant Trials - PUP Studies

PUPs	<u>n</u>	<u>prevalence</u>	<u>high response</u>
Kogenate	64	18 (28%)	10 (16%)
Recombinate	72	22 (30%)	7 (10%)
ReFacto	101	32 (32%)	16 (16%)

Are recombinant products, made in animal cells, structurally altered?
Natural history of inhibitors

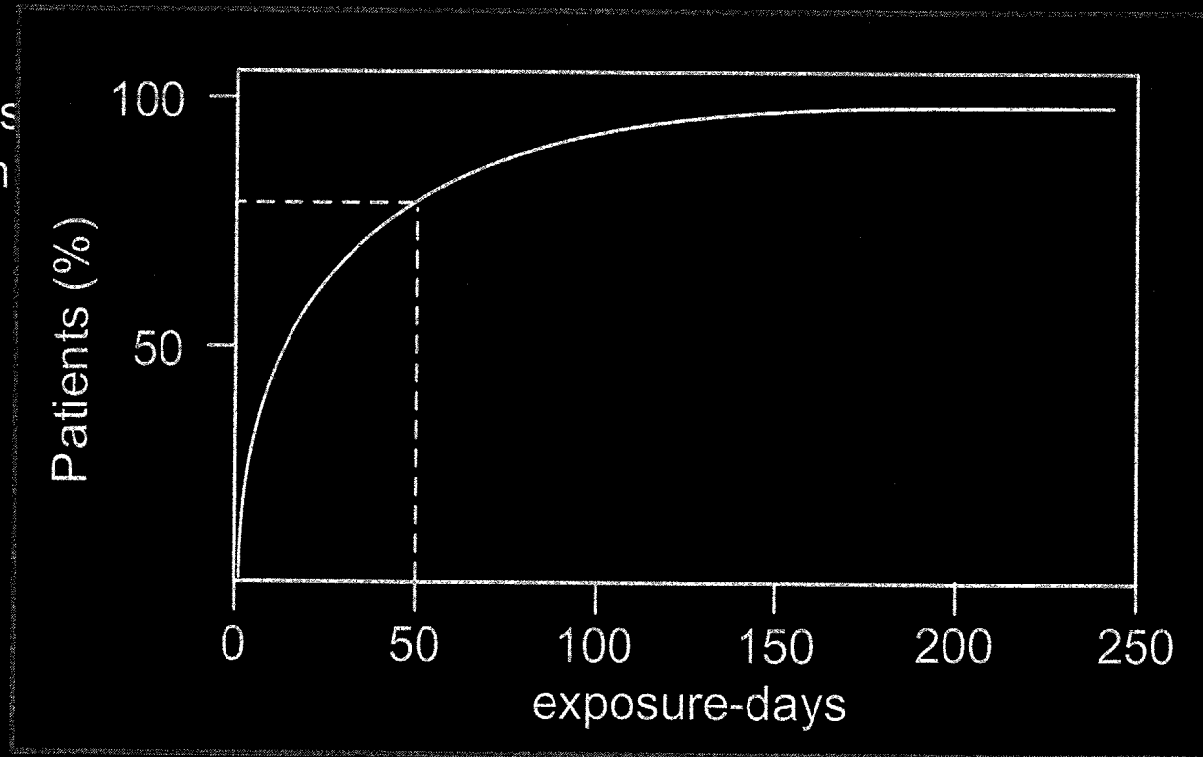
Prevalence of Inhibitors in Recombinant Trials - PTP Studies

PTPs	<u>n</u>	<u>prevalence</u>
Kogenate	86	2 (2%)
Recombinate	69	2 (3%)
ReFacto	113	1 (1%)
Kogenate-FS	71	1 (1%)

PTPs and Immunogenicity

Previously treated hemophiliacs with >250 exposure-days have shown themselves to be tolerant to exogenous factor VIII or IX and are therefore at low risk to develop inhibitors

Any increase
neoantigen



ISTH Recommendation

Recommendation of the SSC scientific subcommittee on factor VIII and factor IX -

Use PTPs with >250 ED to assess efficacy and immunogenicity of new products; use PUPs and NIPs to assess viral safety of new products

White, et al., Utilization of previously treated patients (PTPs), non-infected patients (NIPs), and previously untreated patients (PUPs) in the evaluation of new factor VIII and IX concentrates. *Thrombosis Haemostas* 81:462, 1999

ISTH Recommendation

Recommendation of the SSC scientific subcommittee on factor VIII and factor IX -

High response inhibitor ≥ 5 BU

Low response inhibitor < 5 BU

White, et al., Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX. Thrombos. Haemostas. 85:560, 2001

Post-Marketing Inhibitor Surveillance

